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Original Article

Objective sleep interruption and reproductive hormone dynamics in the menstrual cycle

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ABSTRACT

Objectives: Women report greater sleep disturbance during the premenstrual phase of the menstrual cycle and during menses. However, the putative hormonal basis of perceived menstrual cycle-related sleep disturbance has not been investigated directly. We examined associations of objective measures of sleep fragmentation with reproductive hormone levels in healthy, premenopausal women.
Methods: Twenty-seven women with monthly menses had hormone levels measured at two time points during a single menstrual cycle: the follicular phase and the peri-ovulatory to mid-luteal phase. A single night of home polysomnography (PSG) was recorded on the day of the peri-ovulatory/mid-luteal-phase blood draw. Serum progesterone, estradiol, and estrone levels concurrent with PSG and rate of change in progesterone (PROGslope) from the follicular blood draw to PSG were correlated with log-transformed wake after sleep onset (lnWASO%) and number of wakes/hour of sleep (lnWake-Index) using linear regression.
Results: Sleep was more fragmented in association with a steeper PROGslope (lnWASO% $p = 0.016$; lnWake-Index $p = 0.08$) and higher concurrent estrone level (lnWASO% $p = 0.03$; lnWake-Index $p = 0.01$), but the effect of estrone on WASO was lost after accounting for PROGslope. WASO% and Wake-Index were not associated with concomitant progesterone or estradiol levels.
Conclusions: A steeper rate of rise in progesterone levels from the follicular phase through the mid-luteal phase was associated with significantly greater WASO, establishing a link between reproductive hormone dynamics and sleep fragmentation in the luteal phase of the menstrual cycle.

1. Introduction

Studies in premenopausal women have documented more subjective sleep disruption during the week preceding menses [2], and during menses [2], coinciding with fluctuating levels of progesterone and estrogens. Sleep complaints include longer sleep-onset latency, lower sleep efficiency, and worse sleep quality during the mid-luteal through late luteal phase compared with the mid-follicular phase [1] and lower subjective sleep quality [1,2] during the late luteal phase and menses compared with the mid-follicular, ovulatory, and early/mid-luteal phases. In general, the few polysomnographic studies that have examined sleep at different phases of the menstrual cycle in young, healthy women with no sleep complaints have found that sleep efficiency remains high and relatively stable across the menstrual cycle [3–6], although at least one small study detected higher arousal indices and more wake after sleep onset in a sample of 12 healthy young women studied during the mid-luteal through late luteal phase [7].

While these studies have linked sleep disturbance and changes in sleep architecture to the mid-luteal through late luteal phase, fluctuations in reproductive hormones, including declining levels of estradiol and progesterone prior to menses, were assumed but not measured. Sleep quality has not been examined specifically in relation to reproductive hormone levels or their trajectories. The subjective and objective observations of reduced sleep quality during the mid-luteal through late luteal phase suggest that progesterone plays a critical role, but levels of estrogens also rise and fall in the luteal phase, raising the possibility that both of these reproductive hormones may adversely affect luteal-phase sleep quality. As a result, it is not clear how mid-luteal-phase through late luteal-phase worsening of sleep quality relates to specific hormone levels

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or the rate of change in reproductive hormone levels across the menstrual cycle.

During an ovulatory menstrual cycle, progesterone is monotonic, produced only by the corpus luteum after ovulation and rising during the luteal phase until levels peak mid-luteally, and then decline during the late luteal phase [8]. Progesterone is responsible for the luteal-phase increase in core body temperature of 0.3–0.6 °C [9], a level of elevation in core body temperature that has been shown to fragment sleep [10]. Therefore, the effect of progesterone on body temperature is a putative mechanism by which progesterone could disturb sleep. Progesterone is also a $GABA_A$ receptor agonist [11] that has been shown to increase non-rapid eye movement (NREM) sleep [12,13]. Indeed, observations of increased sleep disturbance in the mid-luteal through late luteal phase have been attributed to changing levels of progesterone [14], although the relationship has not been studied empirically.

In contrast to progesterone, estradiol rises and falls twice during the menstrual cycle: first, during the late follicular phase prior to ovulation and then, again, during the luteal phase [8]. Estrone is a weaker estrogen produced and stored in the adipose tissue [15], rather than the ovary, that mirrors the biphasic dynamics of estradiol, the most potent estrogen. Unlike progesterone, estrogens decrease core body temperature in the absence of progesterone [16], which may protect against sleep disruption. However, data bearing on the effect of estrogens on sleep quality are mixed with estrogen therapy shown to improve sleep quality in postmenopausal women with hot flashes [13,17–21] but also to disrupt sleep by decreasing rapid eye movement (REM) and NREM sleep in ovariectomized rodents [22].

The primary aim of this study was to examine the association of objective measures of sleep fragmentation during the luteal phase in healthy premenopausal women in relation to concurrent levels of progesterone and the rate of change in progesterone from the follicular to mid-luteal phase. We hypothesized that higher progesterone levels as well as a steeper increase in progesterone would be associated with more sleep fragmentation. Our second, exploratory aim was to examine associations of sleep measures with concurrent levels of estrogens (estradiol and estrone), given the inconsistencies in the literature on estrogens' effects on sleep and the gap of knowledge about the impact of physiologic levels of estradiol and estrone on sleep in premenopausal women.

2. Methods

2.1. Participants

Healthy premenopausal women aged 18–45 with monthly menstrual cycles (defined as every 23–35 days for the past 6 months) were recruited from the community to an experimental study where leuprolide was used to induce hot flashes and to study changes in sleep and mood occurring secondary to hot flashes (Clinicaltrials.gov Identifier: NCT00455689 [23]). The current analysis is based on the PSG and serum hormone data obtained at baseline before leuprolide was administered.

Women were excluded if they were pregnant, had a sleep disorder diagnosis confirmed with in-laboratory screening PSG ($n = 1$ excluded for obstructive sleep apnea, $n = 1$ for periodic limb movement disorder), worked a night-shift job, reported experiencing hot flashes, had a current or prior history of psychiatric illness or substance-use disorders confirmed on structured psychiatric assessment, had abnormal screening blood tests (hemoglobin, thyroid-stimulating hormone, prolactin, renal or liver function), or had body mass index (BMI) >35 kg/m^2. A Montgomery–Åsberg Depression Rating Scale (MADRS) score <10 was required to exclude those with depressive symptoms. Women taking or recently using prescription or over-the-counter centrally active medications (antidepressants, anxiolytics, hypnotics, or the anticonvulsant gabapentin) or systemic hormone medications (e.g., birth control pills) were excluded. All participants provided written informed consent and this study was approved by the Partners HealthCare Institutional Review Boards.

2.2. Sleep measures

Prior to mid-luteal administration of leuprolide, participants completed two nights of home PSG scheduled between the peri-ovulatory and mid-luteal phase of the menstrual cycle. Data from the second home PSG were used in the present analyses because hormone levels were obtained concurrent with the second PSG. PSG studies were not obtained during the follicular phase.

PSGs were conducted with the Compumedics Safiro (Charlotte, NC, USA) using standard procedures to define sleep staging, including electroencephalogram (EEG), bilateral electro-oculogram, and bilateral submentalis electromyogram [24]. Respiratory and electrocardiography (ECG) signals were not measured. Concurrent with PSG, participants wore a time-synched actigraph with an event marker to record lights-out and lights-on time.

All records were visually scored in 30-s epochs by the Harvard Polysomnography Core using American Academy of Sleep Medicine (AASM) criteria [24]. The primary measures of sleep fragmentation were: (1) WASO as a percent of sleep period time and (2) the number of awakenings per hour of sleep. Awakenings were defined as alpha EEG activity comprising >15 s of a 30-s epoch. Stage N1 percent, Stage N2 percent, Stage N3 percent, REM percent, and sleep efficiency were also obtained.

2.3. Hormone measurements

Participants were followed closely across one menstrual cycle, from the first day of menstrual bleeding until the mid-luteal phase. Leuprolide was administered approximately 7 days after ovulation, which was determined by an increase in basal body temperature and urinary luteinizing hormone. Blood was drawn first in the follicular phase ("follicular") and then concurrent with the PSG ("concurrent"), which was obtained between the peri-ovulatory and mid-luteal phase before the leuprolide injection based on logistic considerations. As a result, the interval between the blood draw at the PSG and the preceding follicular-phase draw varied.

Blood samples were assayed for serum progesterone (PROG), estradiol (E2), and estrone (E1) at both time points. We calculated the rate of change in progesterone between the two blood draws over the intervening time interval (PROGslope) to determine the rate of increase in progesterone leading up to the PSG. Slope was not calculated for E2 or E1 because estrogens are biphasic between the two time points that were measured.

2.4. Hormone assays

Serum progesterone was measured by automated immunoassay (ARCHITECT®, Abbott Diagnostics, Chicago, IL, USA) [25]. The minimum reportable concentration of this test is 0.1 ng/mL. The inter-assay coefficients of variation (CVs) are 5.2%, 3.8%, and 3.5% for quality-control sera containing 0.7, 6.9, and 16.7 ng/mL, respectively. The reference ranges for women with regular menstrual cycles are follicular phase <0.1–0.3 ng/mL and luteal phase 1.2–15.9 ng/mL.

Estradiol and estrone were measured using liquid chromatography, tandem mass spectrometry (Mayo Clinic, Rochester, NY, USA) [26,27]. The inter-assay CV ranges for estradiol and estrone in the low range studied were 8.6% and 8.7%, respectively [26].

2.5. Statistical analyses

We used SPSS Version 19 (IBM, Chicago, IL, USA) for data analysis. Shapiro–Wilk tests were used to evaluate the normality of the distributions of our dependent variables. Neither WASO% (Shapiro–Wilk = 0.191, $p = 0.013$) nor Wake-Index (Shapiro–Wilk = 0.174, $p = 0.035$) was normally distributed, so these measures were transformed using the natural log function. Differences in sleep measures between women who did and did not have a luteal rise in progesterone at the time of the PSG were examined with Mann–Whitney *U* tests. Simple linear regressions examined associations of sleep fragmentation (lnWASO% and lnWake-Index) from the PSG with concurrent PROG, E1, and E2 levels as well as with PROGslope leading up to the PSG. Given the concomitant changes in reproductive hormones during the luteal phase, multiple linear regression models were developed to determine the relative impact of hormones associated with sleep fragmentation in adjusted analyses (i.e. concurrent E1 and PROGslope) on PSG sleep. Model fit was assessed, including checks for normally distributed residuals and absence of outliers or highly influential observations [28]. Alpha $\leqslant 0.05$ was considered statistically significant. A similar approach was used for secondary exploratory analyses of other standard PSG sleep measures (N1%, N2%, N3%, REM%, sleep efficiency, and sleep onset latency).

3. Results

3.1. Subject demographics, sleep characteristics, and hormone levels

Of 29 women who completed the parent protocol, data for the current analysis were available in 27 subjects who had hormone data concurrent with the PSG. Participants had a mean ± standard deviation (SD) age of 26.9 ± 6.6 years, and were racially diverse (17 white, five black, and five other race or multiracial women). Average BMI was 25.8 ± 4.9 kg/m^2; five women had a BMI between 25 and 30 kg/m^2 (overweight), and six women were obese with a BMI >30 kg/m^2. Age, race, and BMI were not associated with Wake-Index or WASO.

Overall, we observed minimal sleep disturbance in this sample of young healthy women (Table 1) with high sleep efficiencies and expected sleep stage distributions consistent with normative values reported for young adults [29]. Overall, the median WASO was 11.5 min (interquartile range (IQR) 7–21) and the median number of awakenings was 15 (IQR 9–22), translating into a median WASO% of 2.7% (IQR 1.7%–4.7%) as a proportion of sleep period time and median Wake-Index of 1.9 (IQR 1.3–2.9) wakes per hour.

The PSG and concurrent blood draw were obtained on a median menstrual cycle day of 18 (IQR 15–20). The follicular draw was obtained on a median menstrual cycle day of 5 (IQR 3–6). The time interval between the follicular draw and the PSG/concurrent draw was therefore a median of 13 days (IQR 10–15). PROG levels were $\leqslant$1 ng/dL in all participants during the follicular draw and >3 ng/dL in 16 (59.3%) participants (mean (SD) = 10.5 (6.2) ng/dL) at the time of the PSG, reflecting the mid-luteal phase of an ovulatory cycle. The remaining 11 (40.7%) participants completed their PSG peri-ovulatory and therefore their concurrent PROG level was <1 ng/dL because it had not yet risen. Among those with an increase in PROG between time points, the PROGslope showed a mean (SD) increase of 0.70 (0.40) ng/dL per day. Sleep measures for the groups of women who did and did not have a luteal rise in progesterone at the time of the PSG are shown in Table 2. Compared to women whose progesterone had not increased, women whose progesterone levels had risen had significantly higher N2% ($p = 0.045$) and a tendency ($p = 0.068$) for shorter total sleep times.

Mean (SD) estradiol and estrone levels concurrent with the PSG were 112.1 (61.0) and 80.7 (40.7) pg/ml, respectively.

3.2. Associations of concurrent progesterone levels and progesterone slope with sleep fragmentation

Concurrent PROG was not associated significantly with WASO% or Wake-Index (see Table 3).

A steeper increase in PROG leading up to the PSG was associated with higher WASO% (lnWASO% vs. PROGslope: $\beta = 0.64$, 95% confidence interval (CI) 0.1–1.1, $p = 0.016$; see Fig. 1a). Results were consistent in a subgroup analysis ($n = 16$) restricted to women whose PROG increased between the time points (lnWASO% vs. PROGslope: $\beta = 0.63$, 95% CI −0.09 to 1.3, $p = 0.08$). There was a statistical trend for an association between a steeper increase in the PROGslope and a higher Wake-Index (lnWake-Index vs. PROGslope: $\beta = 0.36$, 95% CI −0.06 to 0.78, $p = 0.08$; see Fig. 1b). Thus, for each 0.1-ng/dL increase in the progesterone slope, the proportion of sleep time comprised of WASO increased by 8.9% and the number of wake episodes increased by 4.3 awakenings per hour.

Because the PROGslope calculation included a variable number of follicular phase days during which the progesterone levels were low (median = 10 days, IQR = 7–13), we conducted a sensitivity analysis of PROGslope in relation to lnWASO% and lnWake-Index after adjusting for the number of follicular days. Results were consistent with the overall findings for WASO (lnWASO% vs. PROGslope: $\beta = 0.64$, 95% CI 0.12–1.15, $p = 0.02$) and Wake-Index (lnWake-Index vs. PROGslope: $\beta = 0.37$, 95% CI −0.06 to 0.80, $p = 0.09$).

There was no association between concurrent PROG or PROGslope with the other PSG measures listed in Table 1, including sleep-onset latency (data not shown).

3.3. Associations of concurrent levels of estradiol and estrone with sleep fragmentation

Concurrent E2 levels were not associated significantly with WASO% or Wake-Index (see Table 3) or with the other PSG measures listed in Table 1, including sleep-onset latency (data not shown).

Table 1
Summary of polysomnographic sleep measures from one night of home polysomnography in 27 premenopausal women with regular menses.

Measure	Mean	Standard deviation	Median	Interquartile range
Total sleep time (min)	434	91	438	345–496
Sleep latency (min)	18	21	11	7–22
Sleep efficiency (%)	91.6%	5%	92.0%	91–95%
Stage N1%	5%	3%	4%	3–6%
Stage N2%	48.9%	8.9%	49.0%	43–56%
Stage N3%	18.1%	6.9%	18.0%	14–23%
Stage REM%	25.2%	6.0%	24.0%	22–28%
WASO%	3.5%	2.9%	2.7%	1.7–4.6%
# of awakenings/hr of sleep	2.3	1.3	1.9	1.3–2.9

WASO% = minutes of wakefulness/sleep period time.

Table 2
Home polysomnographic sleep measures in participants with and without progesterone elevation.

Measure	Participants with an increase in progesterone, mid-luteal (n = 16)			Participants without an increase in progesterone, peri-ovulatory (n = 11)		
	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR
Total sleep time (min)*	403 (75)	394	342–478	478 (96)	472	428–577
Sleep latency (min)	22 (26)	13	6–21	14 (10)	10	8–22
Sleep efficiency (%)	90.6 (5.9)	92.0	90.3–94.8	92.9 (4.1)	93	92–96
Stage N1%	4.8 (2.7)	4.0	3.0–5.8	5.5 (3.0)	5.0	3.0–6.0
Stage N2%**	51.3 (9.8)	52.5	48.3–56.8	45.5 (6.4)	44.0	40.0–50.0
Stage N3%	16.5 (6.9)	18.0	13.3–19.8	20.4 (6.5)	18.0	15.0–27.0
Stage REM%	24.4 (6.9)	23.0	20.3–27.8	26.4 (4.5)	25.0	23.0–29.0
WASO%	3.5 (2.1)	2.8	2.1–4.8	3.5 (3.9)	1.8	1.2–4.5
Wake index	2.4 (1.1)	2.3	1.5–3.2	2.2 (1.5)	1.8	1.1–2.8

WASO% = minutes of wakefulness/sleep period time.
Wake Index = number of awakenings per hour of sleep.
* Independent Samples Mann–Whitney U Test $p < 0.10$.
** Independent Samples Mann–Whitney U Test $p < 0.05$.

Table 3
Associations between hormone levels and polysomnographic sleep fragmentation.

Hormone Measure	n	ln WASO%				lnWake-Index			
		β	95% CI	p	R^2	β	95% CI	p	R^2
Concurrent progesterone (ng/dL)	27	0.019	−0.025 to 0.062	0.38	0.031	0.013	−0.020 to 0.047	0.42	0.027
Progesterone slope (ng/dL per day)	23	0.635	0.13–1.1	0.02	0.248	0.364	−0.06 to 0.78	0.08	0.134
Concurrent estradiol (pg/ml)	27	0.002	−0.002 to 0.006	0.27	0.070	0.002	−0.002 to 0.005	0.33	0.057
Concurrent estrone (pg/ml)	27	0.008	0.001–0.015	0.03	0.180	0.007	0.002–0.012	0.01	0.223

lnWASO% = natural log transformation of WASO as a percent of sleep period time.
lnWake-Index = natural log transformation of the number of awakenings per hour of sleep.
Progesterone slope = change in progesterone level subtracting follicular draw from concurrent/PSG2 divided by number of days between blood draws.

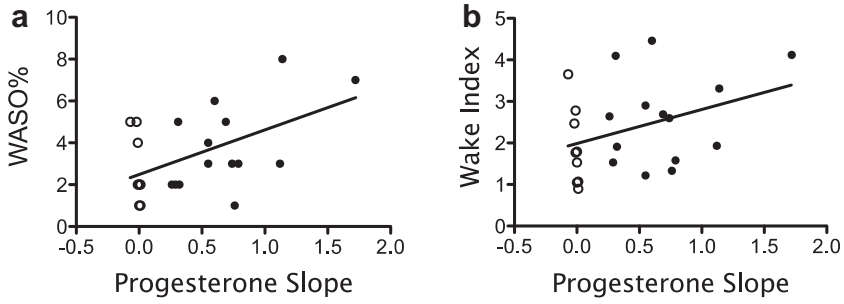

Fig. 1. A steeper increase in progesterone slope was associated with more wakefulness after sleep onset (1a, $p = 0.016$) and more awakenings per hour of sleep (1b, $p = 0.08$). Dark circles indicate women with an elevated serum progesterone level at the time of PSG and open circles indicate women whose serum progesterone level had not yet risen. WASO% = minutes of wake after sleep onset ÷ sleep period time X 100. $n = 23$ (slope could not be calculated in four women because of missing progesterone levels at blood draw 1).

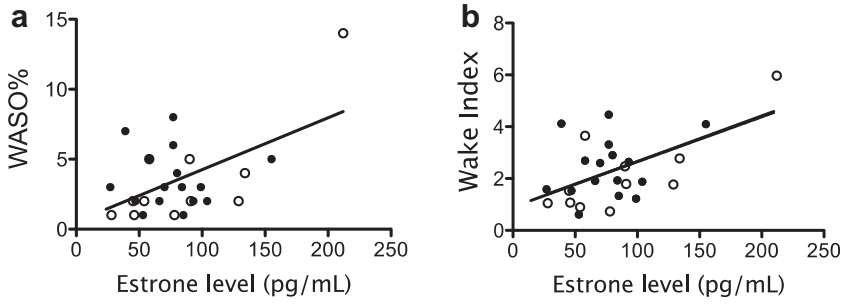

Fig. 2. A higher estrone level was associated with higher WASO% (2a, $p = 0.03$) and more awakenings per hour of sleep (2b, $p = 0.01$). Dark circles indicate women with an elevated serum progesterone level at the time of PSG and open circles indicate women whose serum progesterone level had not yet risen $n = 27$.

Higher E1, concurrent with the PSG, was associated with higher WASO% (lnWASO% vs. E1: $\beta = 0.008$, 95% CI 0.001–0.015, $p = 0.03$; see Fig. 2a) and higher Wake Indices (lnWake-Index vs. E1: $\beta = 0.007$, 95% CI 0.002–0.012, $p = 0.01$; see Fig. 2b). Thus, for each 1-pg/ml increase in the concurrent E1 level, the proportion of sleep time comprised of WASO increased by 0.8% and the number of wake episodes increased by 0.7 awakenings per hour. Because E1was correlated with higher BMI ($r = 0.41$, $p = 0.03$) and is produced and stored in adipose tissue [15], we examined whether BMI was driving the association of E1with WASO% and Wake-Index. BMI correlated weakly with WASO% ($r = 0.31$, $p = 0.12$) and Wake-Index ($r = 0.23$, $p = 0.25$). Adjustment for BMI did not attenuate the significant associations between these sleep measures and concurrent E1 (WASO%: $\beta = 0.008$, 95% CI 0.000–0.015, $p = 0.05$; Wake-Index: $\beta = 0.007$, 95% CI 0.001–0.013, $p = 0.02$).

3.4. Adjusted analyses of progesterone slope and concurrent estrone in relation to sleep fragmentation

A multiple linear regression model that included PROGslope and E1 showed significant independent effects of PROGslope ($\beta = 0.44$, 95% CI 0.05–0.83, $p = 0.03$) and E1 ($\beta = 0.006$, 95% CI 0.000–0.012, $p = 0.04$) on Wake-Index. For WASO%, the association with a steeper PROGslope remained strong after adjustment for E1 ($\beta = 0.704$, 95% CI 0.21–1.20, $p = 0.008$), but the contribution of E1 was attenuated ($\beta = 0.005$, 95% CI −0.002 to 0.013, $p = 0.13$).

4. Discussion

These results demonstrate that objective sleep interruption during the peri-ovulatory through mid-luteal phase of the menstrual cycle is proportionate to the preceding rate of rise in progesterone levels. These findings provide important biological evidence that changing levels of progesterone in cycling women are associated with objective sleep disturbance. Consistent with prior studies of PSG sleep quality in the follicular and luteal phases [3–6], we found no differences in sleep disruption when we examined our sample, solely based on whether participants had or had not yet experienced a luteal-phase increase in progesterone. However, none of the previous studies measured hormone levels across the menstrual cycle, whereas our study results show specifically that the rate of rise in progesterone predicts the amount of mid-luteal-phase sleep fragmentation. Variability in the rate of rise in progesterone between women may explain why some women experience sleep interruption during the luteal phase of the menstrual cycle while others do not.

Our approach represents a first attempt to link sleep disturbance occurring during the mid-luteal through late luteal phase [1,2,7] with fluctuating levels of progesterone. Our findings are consistent with data showing worsening of sleep quality in response to a rise in core body temperature, which occurs in cycling women when progesterone levels begin to increase after ovulation [30]. This temperature rise occurs despite the co-occurring luteal-phase increase in estrogens, which have a weaker suppressive effect on core temperature [31]. Thus, we speculate that the thermal response to increasing levels of progesterone may explain the observed deleterious effect of increasing progesterone on sleep continuity. As we did not observe an association between sleep fragmentation and concurrent progesterone levels, it is possible that accommodation to progesterone exposure and sustained temperature elevation ultimately may occur by the mid-luteal phase. In order to investigate the specific contribution of declining levels of progesterone to sleep disturbance reported during the mid-luteal to late luteal phase [1,2], future studies should examine changes in sleep and sleep disturbance in relation to the downward slope of progesterone levels at this time point of the menstrual cycle. It is notable that progesterone can have hypnotic properties when administered to postmenopausal women [13,32] and premenopausal women during the early follicular phase [33], both of which are low estrogen states. In contrast, we observed a fragmenting effect of rising progesterone levels in the context of higher estrogen levels, a finding that emphasizes the importance of considering the overall hormonal milieu. Moreover, our findings related specifically to the rate of progesterone increase highlight the importance of examining sleep in relation to the changing hormone dynamics across the menstrual cycle and suggest that more static cross-sectional analyses of the menstrual cycle phase may not capture the contribution of hormones to sleep quality.

Neither concurrent progesterone nor rate of increase in progesterone was related to other PSG measures (sleep stages, sleep efficiency, sleep latency, or REM latency) in exploratory analyses. However, we observed a higher percentage of N2 sleep among participants who had experienced an increase in progesterone levels at the time of the PSG relative to those with low progesterone levels, consistent with previous findings of elevated N2 sleep [4,5] and sleep spindle activity [4] in the luteal phase. Our findings provide additional evidence that EEG is sensitive to neurohormonal changes that occur across the menstrual cycle. While the absence of an association between progesterone levels and REM sleep may appear inconsistent with studies showing decreased REM sleep in the luteal phase [34–36], direct comparison cannot be made because progesterone levels were not reported in prior studies.

Our results show that higher serum estrone, but not estradiol, levels at the time of the PSG are associated with more wakefulness in healthy premenopausal women, although this association was lost for WASO% after adjustment for the progesterone slope, suggesting that luteal-phase sleep disruption is driven primarily by the rate of change in progesterone. The basis for a selective association with estrone is unclear, although some animal studies suggest differential effects of estrone versus estradiol on neurocognitive and other neural functions [37]. Comparisons with human studies showing therapeutic effects of conjugated estrogens on sleep after menopause [17–20] or with animal studies showing increased activity levels [22] and decreased NREM sleep [38] when ovariectomized rodents receive estradiol or 17 beta-estradiol, respectively, are limited because of the different underlying hormonal milieu and type of estrogen administered in each study.

A major strength of our study is the prospective documentation of menstrual cycle timing when hormone levels were drawn and PSG was completed. Future studies may further advance our understanding of the hormone associations with PSG sleep by standardizing the timing of PSG studies according to specific hormone profiles or experimentally controlling the hormonal milieu to isolate the effect of changing levels of each hormone on sleep quality. A limitation of the current study is that we were unable to determine the contribution of the rate of rise of estrogens to premenstrual sleep quality because the interval of time between our two menstrual time points encompassed two distinct increases and decreases in levels of estradiol and estrone. In addition, while the use of home PSG is advantageous for eliminating sensitivities to sleeping in the laboratory, it can introduce variability in the home sleeping environment as well as the sleep period time, which we accounted for in our analysis. Finally, because our participants had minimal sleep disturbance and no sleep complaints, our results may underestimate the effect of reproductive hormone dynamics on sleep quality for a sleep-disordered population, to whom our findings may not be generalizable.

In conclusion, a more rapid rate of increase in progesterone levels during the mid-luteal phase may explain why some women report sleep disruption during the mid-luteal through late luteal

phase of the menstrual cycle, particularly during the late luteal phase when they may be sensitive to declining levels of progesterone. Variability in the rate of rise and fall of progesterone between women and between cycles for an individual woman may account for the absence of a universal experience of sleep disturbance during the luteal phase in all premenopausal women across all menstrual cycles. Our findings establish a link between reproductive hormone dynamics and sleep fragmentation in the luteal phase of the menstrual cycle and suggest that the progesterone rise occurring in the context of elevated estrogens contributes to premenstrual sleep disruption.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.02.003.

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